Updating of Working Memory in Ecstasy Polydrug Users: findings from fNIRS

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Abstract

Aims/Objectives: Cognitive deficits are now well documented in ecstasy (MDMA) users with type and relative demand of task emerging as important factors. The updating component of executive processes appears to be particularly affected. The study reported here used fNIRS imaging to investigate changes in cortical haemodynamics during memory updating. *Method:* Twenty Ecstasy users and 20 nonusers completed verbal and spatial memory updating tasks while brain blood oxygenation and deoxygenation change was measured using functional Near Infrared Spectroscopy (fNIRS). *Results:* There was no interaction between group and difficulty on the updating tasks, though there was a significant main effect of difficulty on both tasks. The effects of group approached significance on the verbal updating task. There were significant differences in blood oxygenation and deoxygenation change at optodes centred over the right and left DLPFC, with ecstasy users showing greater blood oxygenation than the other groups. *Discussion:* The lack of a behavioural difference on both tasks, but presence of blood oxygenation and deoxygenation changes in letter updating provides support for the notion that ecstasy-polydrug users are investing more effort to achieve the same behavioural output. Total lifetime dose was high, and recency of use was significantly related to most changes, suggesting that heavy and recent use may be particularly detrimental.

Introduction

While cognitive deficits are now well documented in ecstasy users (Montgomery et al., 2005; Montgomery et al., 2010; Nulsen et al., 2011; Parrott, 2013; Reay et al., 2006), some studies report non-significant behavioural differences (Halpern et al., 2011; Roiser et al., 2007). However, recent research suggests that even in the absence of behavioural differences, there may be cognitive reallocation and changes in brain function (e.g. Burgess et al., 2011; Daumann et al., 2003; Jacobsen et al., 2004; Roberts et al., 2013a; Roberts et al., 2013b; Roberts et al., 2013c). Theoretical models of executive functioning have attempted to fractionate the central executive based on latent variable analysis of performance on executive function tasks. One of the most widely accepted frameworks proposed by Miyake et al. (2000) fractionate the central executive in to 3-component processes: shifting (the ability to shift attention back and forth between different tasks), inhibition (the ability to inhibit an automatic response) and updating (the ability to monitor and update the contents of working memory). One of the most consistent executive deficits in ecstasy users is degradation of the updating process which requires monitoring and coding incoming information, assessing its relevance, and reviewing/amending the contents of working memory accordingly. The fundamental nature of memory updating is that it requires active manipulation of relevant information, rather than acting as a short-term store (Lehto, 1996; Miyake et al. 2000; Morris & Jones, 1990). Moreover, as the usefulness of working memory as a whole is related to the efficiency with which we maintain, monitor, and edit the online contents, the updating component is one of the most often used functions in cognition (Carretti et al., 2005).

Previous research shows that ecstasy users appear to be impaired in memory updating, especially if key indicators of Miyake et al.'s (2000) executive framework are used. Montgomery et al. (2005) assessed updating using a running letter memory task and computation span, with ecstasy users performing significantly worse than non-users on both tasks. This was replicated by Montgomery and Fisk (2008), where ecstasy users not only performed worse on the memory

updating task, but indices of ecstasy use were also significantly related to performance (with heavier users exhibiting more impairment). Wareing et al. (2004) used computation and reading span tasks, analogous to Miyake et al.'s operation span task. Although no group differences were observed on the reading span measure, ecstasy users were significantly impaired on computation span. This was replicated by Fisk et al. (2004), where group differences in computation span remained significant after controlling for the use of other drugs, indicating that in this study memory updating performance was related to the use of ecstasy, and not other substances. However, some similar span tasks have shown no relation to ecstasy use (Dafters et al., 1999) and variants of the n-back task have also shown mixed results (Alting von-Geusau et al., 2004; Gouzoulis-Mayfrank et al., 2003). Daumann et al. (2003) used a 0-back, 1-back and 2-back condition. Again, there were no significant differences in terms of correct responses and reaction times between pure ecstasy users and polyvalent ecstasy users. In terms of fMRI activation during the 1-back task, polyvalent ecstasy users did not differ significantly from controls, however pure ecstasy users presented lower activations than controls in the inferior temporal and angular regions; additionally, pure users had lower signal changes in the striate cortex, and a higher BOLD response in the premotor cortex compared to polyvalent users. Similarly, during the 2-back condition, pure users showed lower activation in the angular gyrus. This suggests that while behavioural differences may not be present, there may be some changes in neural activation that mask these differences. A further study also found evidence for abnormal activation in the left hippocampus of 6 ecstasy users relative to 6 nonusers, which significantly negatively correlated with length of abstinence from ecstasy, indicating that as abstinence increased, the functioning of the inhibitory circuits of the hippocampus recovered (Jacobsen et al., 2004).

A number of other studies have found that ecstasy users and nonusers perform comparably on tests believed to tap the updating executive component process. Using backward digit span no performance differences have been observed in many studies (Bhattachary & Powell 2001; Gouzoulis-Mayfrank et al., 2003; McCardle et al., 2004; Thomasius et al., 2003). Gouzoulis-Mayfrank

et al. (2000) found that ecstasy/cannabis users performed worse than nonuser controls. They were not impaired relative to cannabis only users (matched for cannabis use), and cannabis only users did not differ significantly from controls. Cumulative lifetime ecstasy dose and age of onset of cannabis use were significantly correlated with performance on this task. Thus it appears that some aspect of cannabis use may also affect performance on this task. This was supported by Croft et al. (2001) where no performance differences were observed between ecstasy/cannabis users, cannabis only users and drug-naïve controls on the backward digit span task. However, after forming a single drug-using group (comprising of ecstasy/cannabis and cannabis only users), this group performed worse than controls, which the authors propose was more related to the use of cannabis rather than ecstasy. Using Backward Digit Span (BDS), Reay et al. (2006) found no performance differences between groups after controlling for the use of cannabis, cocaine, alcohol and tobacco. Similarly, Nulsen et al. (2011) observed no main effect of group and little predictive power of MDMA variables in regression analyses on BDS. Halpern et al. (2011) measured BDS in ecstasy users who had little "other drug" experience and non-users; ecstasy users performed worse than nonusers, though there was no effect of level of use and the results were subsequently rejected as too modest to demonstrate ecstasy related effects. Bedi and Redman (2008) used BDS and found no differences between cannabis polydrug, ecstasy polydrug and nonusers, though there were some weak negative semi-partial correlations between performance and lifetime ecstasy dose and LSD dose. In addition, a number of prospective cohort studies from Wagner and co-workers (Wagner et al., 2013; 2015a; 2015b) have found no differences between ecstasy users and nonusers in BDS at baseline, follow up, and no relationship between ecstasy use parameters and performance.

Subtracting Serial Sevens (SSS) has been used by Curran and co-workers who found ecstasy users make significantly fewer subtractions than nonusers on this task (Curran & Travill 1997; Curran & Verheyden 2003), while Morgan et al. (2002) found that ecstasy users made significantly more errors on the task. In addition, Verdejo-Garcia et al. (2005) used a combined measure of updating and found that ecstasy use was an important contributory factor in deficits in working memory

updating among a clinical sample of poly-substance abusers. Indeed, severity of ecstasy use was the best predictor of performance on this dimension.

In addition to behavioural measures, the present study uses functional Near Infrared Spectroscopy (fNIRS) to assess cognitive function. fNIRS is an optical neuroimaging technique that assesses cortical haemodynamic changes in response to cognitive demand (Ayaz et al., 2012). Infrared light is transmitted into the PFC at two wavelengths (850nm and 730nm), allowing estimation of oxygenated (oxy) and deoxygenated haemoglobin (deoxy-Hb). This makes fNIRS an appropriate imaging tool for investigating executive functioning. As neuronal activity and haemodynamic response are coupled, increases in neuronal activity can be inferred by an increase in oxy-Hb (Leff *et al.,* 2011). The location of the activation is regionally specific, and thus the area of the cortex underlying a given optode is responsible for the observed oxy/deoxy-Hb changes there (Leff *et al.,* 2011). The changes in oxy and deoxy-Hb differ in terms of what they reflect about cortical haemodynamics. An increase in Oxy-Hb from baseline levels infers an increase in blood flow – as an area becomes more active, an increase in glucose and oxygen utilisation results in an increase in the transport of both of these substances to an area of the brain and a subsequent surplus of oxygenation (Bunce et al., 2006; Fox et al., 1998). An increase in deoxy-Hb infers changes in oxygen utilisation in a particular area of the brain – as oxygen is withdrawn from the oxygenated haemoglobin to be used in the task at hand, there is a resultant increase in deoxy-Hb (Obrig & Villringer, 2003). Previous research from our own group (Roberts et al., 2015) has shown that ecstasy users perform comparably to nonusers on a multitasking paradigm but have increased oxygen utilisation while performing the task.

In summary, previous studies investigating memory updating in ecstasy users exhibit equivocal results. However, studies that utilised key indicators of Miyake et al.'s (2000) framework usually elucidated between-group differences. It was therefore predicted that ecstasy-polydrug users would perform worse than nonusers on spatial and letter updating tasks. In line with previous

studies showing changes in cortical haemodynamics during task performance, it was also predicted that ecstasy-polydrug users would have increased prefrontal cortical blood oxygenation change and increased deoxygenation change relative to nonusers.

Design:

For analysis of behavioural data and fNIRS data a between groups design was used. The between groups factor was drug user group which consisted of 2 levels (Ecstasy users and drug naïve controls). Mixed ANOVA was performed on the behavioural data for both letter updating and spatial updating, with user group as between groups, list length (difficulty) as within and the scores as the dependent variables. The fNIRS data was analysed with univariate ANOVAs using mean oxy and deoxy-Hb changes from baseline as the dependent variables at the 4 different areas as detailed in the methods below.

Participants:

Twenty ecstasy users (mean age = 21.76, SD = 3.19, 11 = male), and 20 drug naïve controls (mean age = 19.68, SD = 1.89, 9 = male) were recruited via direct approach (e-mail) to University students. Participants were required to be between 18 – 29 years of age. For inclusion in the ecstasy/MDMA user group, participants must have used ecstasy/MDMA on at least 5 occasions over their lifetime (actual minimum = 6 tablets; mean total lifetime dose 1305.31 ±4951.61 tablets; average amount used in last 30 days – 3.8 ±4.63 tablets; frequency of use – 0.39 ±0.48 time per week) although they may have used a range of substances in addition to MDMA. For inclusion in the drug naïve control group participants must have never consumed any illicit drugs.

Participants were asked to abstain from consuming ecstasy for a minimum of 7 days prior to testing. Participants were also requested to abstain from use of other illicit drugs for a minimum of 24 hours prior to participating and ideally 7 days (actual abstinence periods are reported in Table 2).

Materials

Background Variables - tasks administered:

The *Background Drug Use Questionnaire* is a self- report measure of drug use and other lifestyle variables. Estimates of total lifetime drug use of each drug consumed were calculated (as per Montgomery *et al.,* 2005) as well as totals for last 30 days drug use. Other background variables including health status, age and years of education were also obtained from this questionnaire.

Several measures of sleep were taken including a *sleep quality questionnaire* which measured typical duration and quality of sleep (how many hours slept typically, how much sleep over the previous 3 nights). The *Epworth Sleepiness Scale* (Johns, 1991) is a measure of subjective daytime sleepiness, which investigates the chances of the individual falling asleep or dozing in various situations – a high score being indicative of greater daytime sleepiness. The *Morningness-Eveningness Questionnaire* (MEQ, Terman *et al.,* 2001), originally developed by Horne & Östberg (1976) is a self-assessment of morningness or eveningness types in human circadian rhythm. A high score is indicative of a morning type, whereas a low score is suggestive of an evening type. Finally the Karolinska Sleepiness Scale (Akerstedt & Gillberg, 1990), is a self-assessment of current sleepiness, and can be administered at different time points of the experiment (before and after completion of tasks) to assess sleepiness. The above indices of sleep were taken to explore the relationship between sleepiness and cognition, and also to observe whether there are any differences between groups in their sleep patterns, as it has been suggested (Cole, et al., 2002) that lack of sleep (amongst other lifestyle variables) may underlie possible cognitive deficits in ecstasy using cohorts.

State Anxiety, Arousal and Hedonic Tone (Depression) were measured using the state mood adjective checklist developed by Fisk & Warr (1996). Participants rated their feelings at the time of testing on a 5 point Likert scale from 1 = not at all, to 5 = extremely on several items related to each subscale. A high score on each subscale indicates increased hedonic tone/anxiety/arousal.

The *NASA TLX (Task Load Index)* (Hart & Staveland, 1988) is a series of visual analogue scales measuring subjective workload post-task. Participants are required to place a mark on a 100mm line to indicate perceived demand of each task on six subscales (mental demand, physical demand, temporal demand, personal performance rating, effort and frustration). This measure was used as it has been suggested that ecstasy users may be more susceptible to stress (Wetherell et al., 2012), and thus report increased cognitive effort.

Raven's Standard Progressive Matrices (Raven et al., 1998) is a measure of fluid intelligence which requires participants to solve a series of problems (5 sets of 12) with increasing difficulty. Symbolic sequences are presented with a part missing, the participant is required to select the correct missing part from 6 possible options. This requires an understanding of the various elements involved and their interactions with one another.

Letter span: Consonants appeared on a computer monitor sequentially and remained on screen for 1.25s each. Following a sequence of letters being presented, participants were required to recall the order in which the letters appeared. To begin with 3 sets of 2 letters are presented, this then progresses to 3 sets of 3 letters, then 3 sets of 4 letters and so on up until 3 sets of 7 letters are presented. Participants' span is noted as the largest string of letters they can recall accurately on at least 2 of the 3 trials.

Spatial span: Analogous to the letter span task, participants have to recall the positions of highlighted blocks in a Corsi block type arrangement in the order that they were presented in. Highlighted blocks appear on screen for 1.25s each.

<u>Updating Tasks</u>

The letter and spatial updating tasks were carried out using a similar procedure to Montgomery and Fisk (2008), whereby each participant's letter and spatial span were first calculated prior to conducting the updating tasks.

Letter updating: Based on running span memory task (Morris & Jones, 1990) consonants appear on the computer screen in random sequences dependent upon the participant's calculated letter span. Twenty-four trials are presented and in each the participants are unaware of the number of letters that will appear in the sequence (length of list). Participants are required to recall the most recent *n* consonants in the order in which they appeared (where *n* is the participants calculated letter span). There are 4 sequence lengths; *n, n* + 2, *n* + 4 and *n* + 6 and 6 trials of each length were presented in randomised order. Points were awarded for a correctly identified letter recalled in the correct position of the sequence.

Spatial updating: This computer-based task was again analogous to the letter updating task. Spatial locations were highlighted on a Corsi block type arrangement in random sequences. Thirty trials were presented and again participants were unaware of the length of the sequence being presented each time, with the exception of 6 trials, in which participants were told how many spatial locations were going to be presented (in each case it was always the participant's span that was the list length for the known length trials). Again, participants were required to recall the last *n* (where *n* is the participants calculated spatial span) positions in the order that they were presented. There were 6 trials at each list length; known *n,* unknown *n, n* + 2, *n* + 4 and *n* + 6 and the order in which these appeared was randomised.

For both tasks, the overall performance scores were a composite of performance on each level of difficulty of the task relative to the participants span divided by the number of levels of difficulty, to give a mean score. For example, if a participant had a span of 5 on the letter updating task, this would yield 5 responses on each trial, therefore for each level of difficulty on the task, their total score would be divided by their span (in this case 5) to give a mean score of performance on each level of difficulty.

<u>Deployment of fNIRS</u>

Changes in prefrontal blood oxygenation were monitored using a continuous wave fNIRS system developed by Drexel University (Philadelphia, PA) and supplied by Biopac systems (Goleta, CA, USA). The sensor had a temporal resolution of 500ms per scan (2Hz), with a source-detector separation of 2.5cm allowing 1.25cm penetration depth (Ayaz *et al.,* 2012). An fNIR100 control box and data acquisition and visualisation software COBI studio (Drexel university) were used during data collection (as per Ayaz *et al.,* 2011; Ayaz *et al*., 2012) with a serial cable between display and acquisition PCs to identify task markers. Raw data from was pre-processed using fnirSoft (Ayaz, 2010). After visually inspecting the data, any saturated channels were discarded. A low-pass filter (0.1Hz cut off) and a linear phase filter (order of 20) were used to remove high frequency noise and noise due to respiration (Ayaz *et al.,* 2011; Ayaz *et al*., 2012). Using the modified Beer-Lambert law logarithm in fnirSoft (Ayaz, 2010), we calculated total blood oxygenation, deoxygenation and volume changes relative to baseline over the entire epoch for the 16 channels. Mean oxy and deoxy-Hb changes from baseline were calculated over the whole task epoch for each channel for the fNIRS data. Following this, optodes were grouped together for analysis, for comparison of regions of the prefrontal cortex (PFC) (Optodes 1, 2, 3 and 4, were grouped together as the left dorsolateral prefrontal cortical (DLPFC) region. Optodes 5, 6, 7 and 8 were grouped together as the left PFC region. Optodes 9, 10, 11 and 12 were grouped together as the right PFC region and Optodes 13, 14, 15 and 16 were grouped together as the right DLPFC region). fNIRS data was analysed using a series of ANOVAs with group as the between groups variable and oxy and deoxy-Hb change for the 4 groups of optodes as the dependent variables.

Procedure

Participants were required to attend the lab for a one off session lasting approximately 2 hours. Testing sessions commenced at 9am, 11.30am and 2pm, equal numbers of each group were tested at each time. Upon entering the lab participants were given an information sheet explaining what was involved in the study and written consent for their participation was obtained. Following this

participants completed a battery of questionnaires in the following order; Background drug use questionnaire, sleep quality questionnaire, morningness-eveningness questionnaire, Epworth sleepiness scale, pre-test Karolinska sleepiness scale, state mood questionnaire and Raven's progressive matrices. Participants then completed the letter span task and the spatial span task, the order in which these were given was randomised. The fNIRS headband was then fitted to the participants' forehead. The fNIRS signals were displayed on a desktop computer running COBI studio (Drexel University) in an adjacent room to the testing room. Providing the signals from the fNIRS sensors were stable, a baseline of inactivity was recorded – this involved participants watching a video of planet earth accompanied with soothing music. Following this the letter updating and spatial updating tasks were completed (a baseline was taken prior to each task). After completing the tasks participants completed the post task Karolinska sleepiness scale and post task NASA TLX (one for each task). Finally participants were fully debriefed and were paid £20 in store vouchers. The study was approved by Liverpool John Moores University Research Ethics Committee, and was administered in accordance with the ethical guidelines of the British Psychological Society.

Statistical analysis

ANOVA was used to test for group differences in the background variables, with mixed ANOVA used for the Karolinska sleepiness scales and MANOVA for the NASA-TLX. Mixed ANOVA was used to analyse spatial and letter updating. A series of univariate ANOVAS and ANCOVAs, incorporating any group differences in background variables were implemented for the fNIRS data. To assess the relationship between indices of drug use and relative oxy and deoxy-Hb change, Spearman's correlations were used.

Results

Socio-demographic information about the participants, sleep measures and scores of anxiety, depression and arousal from the mood scale are shown in Table 1. Indices of other drug and alcohol use are displayed in Table 2.

<<Insert Tables 1 and 2 about here>>

One way ANOVA revealed no significant between group differences on several background variables including total score on letter span, spatial span, the ESS, total score on the MEQ, levels of anxiety, depression and total score on Raven's Progressive Matrices (see Table 1 for F values). However there were between group differences in age $F(1,34) = 5.81$, $p<0.05$ and average number of hours slept per night $F(1,38) = 5.77$, $p<.05$; ecstasy-polydrug users were on average 2 years older than non-users and reported an hour less of sleep per night. In addition, ecstasy-polydrug users also reported lower levels of arousal on the day of testing $F(1,38) = 6.42$, $p<.01$. A mixed ANOVA was used to analyse the Karolinska sleepiness scale pre/post scores. There was no main effect of time, no significant time x group interaction, but a significant main effect of group, indicating that ecstasy-polydrug users felt sleepier prior to testing and after testing $F(1,34) = 12.49$, $p<.001$. A MANOVA on the NASA-TLX scores for letter updating revealed a non-significant main effect $F(6,29) = 0.78$, $p>.05$, and all univariate comparisons were also non-significant. A MANOVA for the NASA-TLX scores on the spatial updating revealed a non-significant main effect $F(6,31) = 1.01$, $p>.05$, though differences in mental demand approached significance $F(1,36) = 3.36$, $p = 0.07$; this indicated that ecstasy-polydrug users found the task more mentally demanding that nonusers.

Inspection of Table 2 shows that the ecstasy-polydrug users consumed a range of substances. If a participant was a regular user of a particular substance, they completed an inventory of prior use. However, if they felt that their use of that substance was occasional (<5 times in total) they did not complete this.[1] Consequently, in addition to means of drug use indices, there are percentages of participants reporting ever having used a substance in Table 2. Univariate ANOVA on average weekly alcohol consumption revealed a significant between group difference $F(1,38) = 5.28$, $p<0.05$, reflecting higher average weekly alcohol consumption in ecstasy-polydrug users.

[1] Participants were asked about their use of: alcohol, amphetamines, cannabis, cocaine, crack cocaine, dimethyltryptamine (DMT), gammahydroxybutyrate (GHB), herbal ecstasy, heroin, ketamine, LSD, mushrooms, amyl nitrate poppers, Prozac, Salvia Divinorum, benzodiazepines, tobacco, Viagra, steroids, any novel psychoactive substances (e.g. mephedrone, naphyrone) and any other substance that they had tried.

Behavioural Data Analysis

Performance on the updating tasks was assessed using mixed ANOVA. Data are displayed in Figure 1. For letter updating, mixed ANOVA with difficulty (4 levels) within groups and group (2 levels) between groups yielded a significant main effect of difficulty indicating that regardless of group, all participants performed worse at the longer list lengths $F(3,36) = 23.82$, $p<.001$. The difficulty x group interaction was non-significant $F(3,36) = 1.09$, $p>.05$, and the main effect of group approached significance $F(1,38) = 2.34$, $p = .07$ (1-tailed). For spatial updating, a mixed ANOVA (in this case difficulty had 5 levels) revealed a significant main effect of difficulty $F(4,34) = 14.21$, $p<.001$. However the difficulty x group interaction was non-significant $F(4,34) = 0.46$, $p>.05$, as was the main effect of group $F(1,37) = 0.06$, $p>.05$.

<<Insert Figure 1 about here>>

fNIRS Analysis

Mean averages of oxygenated and deoxygenated blood changes from baseline across groups, for the updating tasks are displayed in Table 3 and also represented in Figure 2. Univariate ANOVAs were conducted on each region to assess between group differences in blood oxygenation and deoxygenation change from baseline for each task. F values and significance levels for all fNIRS analyses are also displayed in Table 3, and significant effects discussed below.

<<Insert Figure 2 about here>>

Letter Updating:

There were no differences in oxy-Hb change in the LDLPFC, LPFC or RDLPFC during letter updating. There were however significant oxy-Hb changes in the RPFC $F(1,33) = 2.95$, $p<.05$ (1-tailed). Inspection of the means in Table 3 shows that this is because ecstasy-polydrug users show an increase in oxygenation relative to baseline compared to nonusers. Between group differences in deoxy-Hb change from baseline were apparent in the LDLPFC $F(1,33) = 2.70$, $p<.05$ (1-tailed), LPFC

F(1,33) = 6.24, p<.01, RPFC F(1,33) = 6.71, p<.01 and RDLPFC F(1,33) = 6.26, p<.05. Again, ecstasy - polydrug users showed an increase from baseline in deoxy-Hb compared to nonusers. Given the significant differences in some background variables, the analyses were re-run including average hours of sleep per night, age, arousal and the Karolinska sleepiness scale (pre and post) as covariates. All oxygenation changes remained non-significant after removing variance due to these background variables. For deoxygenation change, in the LDLPFC, the difference which approached significance at p = 0.06 was no longer approaching significance, though none of the background variables were significant as covariates (p>.05 in all cases) F(1,28) = 3.03, p = 0.09. In the LPFC, average hours of sleep approached significance as a covariate F(1,28) = 3.12, p = 0.09; ecstasy-polydrug differences remained significant after controlling for all of the background variables F(1,28) = 8.49, p<.01. Differences in RPFC, F(1, 28) = 7.43, p<.01 and RDLPFC, F(1,28) = 7.21, p<.01 remained significant after control for all of the background variables, and no background variables were significant as covariates.

Spatial Updating:

For spatial updating, there were no significant differences in oxygenation change from baseline in any areas, F<1 in all cases. For the deoxygenation change, differences in the LDLPFC approached significance F(1,32) = 1.99, p = 0.08, showing a trend for ecstasy-polydrug users to have greater deoxygenation change. All other difference in deoxy-Hb change were non-significant F<1 in all cases. ANCOVA to control for differences in background variables in spatial updating did not change the statistical significance of the analyses; the difference which was approaching significance for deoxygenation change in the LDLPFC was non-significant after controlling for the background variables F(1,27) = .00, p>.05, though none of the background variables were significant as covariates. For deoxygenation change in the RPFC, arousal was significant as a covariate F(1, 18) = 5.25, p<.05, but the ecstasy-polydrug group differences remained non-significant F(1,18) = 1.07, p>.05.

Correlations with background differences and indices of drug use.

To investigate the role of background variables and recent and cumulative use of "other" drugs on cortical haemodynamics, Spearman's bivariate correlations were used. Significant cortical oxy and deoxygenation changes were correlated with indices of ecstasy, cannabis, ketamine and cocaine use (frequency of use, total lifetime dose, amount used in the last 30 days). In addition, significant differences in the background variables age, alcohol consumption (units per week) and sleep (hours per night) were also correlated with haemodynamic changes. The correlation coefficients are displayed in Table 4.

<Insert Table 4 about here>

Inspection of Table 4 shows that there were no significant correlations with the background variables, or indices or cocaine use, $p>.05$ in all cases. Frequency of ketamine use, frequency, total lifetime dose and recent use of cannabis were positively associated with oxygenation change in the RPFC during the verbal task. For the ecstasy use variables, frequency of use was significantly associated with oxygenation change in the RPFC and deoxygenation change in the LPFC and RPFC. Total lifetime dose of ecstasy was significantly associated with deoxygenation change in the RPFC, and recent use was significantly associated with all significant haemodynamic changes. Where there were significant correlations with indices of more than one drug, the strength of the correlations was compared using an asymptotic z-test (see, Lee & Preacher, 2013). The correlation between frequency of ecstasy use and RPFC oxygenation change was significantly stronger than the correlation with frequency of cannabis use $z = 4.09$, $p<.001$. The correlation between amount of ecstasy used in the last 30 days and RPFC oxygenation was significantly stronger than the correlation with cannabis used in the last 30 days, $z = 2.45$, $p<.01$. There was no significant difference between the strength of the correlations between frequency of ecstasy and ketamine use and RPFC oxygenation, $z = 1.71$, $p >.05$.

Discussion

The present study found little evidence for behavioural impairment of executive function in human ecstasy-polydrug users. Ecstasy-polydrug users did however display differences in cortical blood oxygenation in areas of the prefrontal cortex compared to drug naïve controls, suggesting that their PFC is working harder to achieve the same behavioural response (Ayaz et al., 2011). There were a number of significant correlations with indices of drug use suggesting that level of ecstasy use and cannabis use contribute towards the observed effects.

As stated in the introduction, differences in memory updating are one of the most consistently found executive function deficits in ecstasy-polydrug users (Fisk et al., 2004; Gouzoulis-Mayfrank et al., 2000; Montgomery et al., 2005; Montgomery & Fisk, 2008; Reay et al., 2006; Wareing et al., 2004). However in the present study, there were no group differences in overall performance in running memory. This is not in line with previous research employing this paradigm (e.g. Montgomery & Fisk, 2008). However, inspection of performance in Figure 1 shows that ecstasy-polydrug users had lower mean letter recall (which approached significance) in the verbal running memory task, though not the spatial task. Nonetheless, there were differences in prefrontal blood oxygenation and deoxygenation change during the letter updating task. Differences were seen in the RPFC oxygenation change, and all deoxygenation changes during letter updating. In all cases ecstasy-polydrug users had higher blood oxygenation and deoxygenation change suggesting that they are working harder to achieve the same behavioural outcome. Indeed this has been seen in fMRI studies looking at memory updating, where ecstasy users had differences in activation despite equivalent behavioural performance (Daumann et al., 2003; Jacobsen et al., 2004) and also in EEG studies of other cognitive functions (Burgess et al., 2011). The results also provide further evidence for the possible localisation of ecstasy-related degradation (whether this is temporary or permanent). Salmon et al. (1996) saw an updating-related increase in activation in the mid DLPFC, left middle frontal regions, and the right frontal pole. Similarly, Van der Linden et al. (1999) found the most

significant increases in activation occurred in the left frontopolar cortex spreading to the left middle frontal area during a 4-item running memory task, while Postle et al. (2001)and Collette et al. (2005) both observe that updating tasks consistently activate the DLPFC. Despite the non-significant behavioural differences, ecstasy-polydrug users were showing increases in deoxygenation change in areas of the DLPFC during the task suggesting that it was the process of updating of working memory that was causing an increase in oxygen uptake from the cell and thus a net increase in deoxygenation. If we extrapolate what the increase in deoxygenation change could mean compared to an increase in oxygenation change, the non-significant differences in the latter reflect that there is no overall increase in blood flow to the site (Bunce et al., 2006). However, the significant difference in the former show that oxygenation turnover and utilisation by the cell is greater (Obrig & Villringer, 2003). As such it is possible that a longer paradigm which required continuous updating (e.g. the n-back task) with no inter-trial intervals would yield greater differences in oxygenation change in addition to those observed in deoxygenation change in the present study. Future research should seek to clarify this.

Despite the differences in cortical haemodynamics, in light of the non-significant behavioural differences, it remains a possibility that participants did not follow instructions and failed to adopt an updating strategy as instructed. Ruiz et al. (2005) suggest that a recency strategy is used in running memory tasks (remembering those items that one saw most recently via phonological rehearsal) and have reported clear recency effects on letter and word memory-updating tasks, which are magnified with increasing list length (i.e. the recency strategy was more likely to be used for longer list lengths). However, Morris and Jones (1990) found that memory updating on a running memory task was not affected by articulatory suppression, and consequently concluded that updating was not performed by the articulatory loop but rather by the central executive. Given that Baddeley and Hitch (1993) maintain that recency is a short-term memory phenomenon and is not related to working memory, this does not support the use of a recency strategy in the present study. The lack of list length effects is in line with research in cognitive psychology showing that updating is

an all or nothing process and does not involve a cumulative increase in cognitive demand as list length increases (Fisk & Sharp, 2004).

To investigate the effect of level of drug use on cortical haemodynamics, correlations were performed between indices of drug use and oxy and deoxy-Hb change, with interesting differentiations emerging. The three cannabis use variables that were entered all positively correlated with oxygenation change in the RPFC, with higher use associated with higher oxygenation change. As all of the cannabis users also used ecstasy, this provides evidence of the effect of concomitant use of cannabis on cortical haemodynamics, however in all cases except total lifetime cannabis dose and oxy-Hb change in the RPFC, the correlations with ecstasy use indices were stronger than those with cannabis. Indices of ecstasy use were significantly associated with all changes in cortical haemodynamics; frequency of use with RPFC oxygenation change and LPFC and RPFC deoxygenation change; lifetime dose with RPFC deoxygenation change and recent use with all significant haemodynamic changes. This is in line with recent studies from our own lab where recency of use was a significant predictor of oxy-Hb change during an inhibition task (Roberts & Montgomery 2015a) and a semantic access task (Roberts and Montgomery 2015b). While these correlations with individual indices of drug use are noteworthy, they do not capture the interactive effects of concomitant use of ecstasy and other drugs at the same time. For example, co-use of ecstasy and cannabis is purported to be neuroprotective, through a reduction in hyperthermia (Tourino et al., 2010) while co-use of ecstasy and cocaine is purported to increase MDMA-related oxidative stress (Peraile et al., 2013). Thus there are complex interactions between substances not reflected here, and future research should seek to investigate these. It is also worthy of note that the ecstasy-polydrug users had increases in oxy and deoxy-Hb relative to baseline over almost every area during both tasks. However, for the letter updating task, nonusers had decreased oxy and deoxy-Hb relative to baseline. As increased mental effort is usually accompanied with an increase in brain activation (Gevins & Smith, 2000), it remains a possibility that the nonusers found the task easier than the ecstasy users and did not thus invest mental effort in their performance.

The present study had a number of limitations. As with many studies in this area, the ecstasy users in this sample are polydrug users; thus it cannot be ruled out that these effects result from the co-use of other drugs. Correlations were performed between various indices of drug use and oxy-Hb and deoxy-Hb change. In most cases, correlations with indices of ecstasy use were stronger than those for other drugs, with recency of use emerging as a particularly important factor. The use of self-reported drug use can also be criticised in terms of accuracy, especially given memory deficits that associated with substance use. This method is commonly used in this research area (Montgomery *et al.,* 2005: Roberts *et al.,* 2014). Where objective measures of substance use have been collected in our previous work, low levels of recent use were found in participants' urine, and exclusion of participants with positive screens did not change the significant effects (Roberts *et al.,* 2013).

The present study provided further support for ecstasy-polydrug related changes in cortical haemodynamics during a memory updating task. These changes were present in the absence of behavioural deficits, and it is proposed that the changes reflect increased cognitive effort in ecstasy-polydrug users. Indices of ecstasy use, in particular recency of use, emerged as significant factors in the deficits and future research should seek to clarify the role of recent use in any observed deficits.

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Table 1 – Indices sleep quality, fluid intelligence and socio-demographic variables

	Ecstasy Polydrug Users		Drug Naïve Controls		F(1,38) =
Males: n, %	11 (55)		9 (45)		
	Mean	**SD**	**Mean**	**SD**	
Age	21.76	3.19	19.68	1.89	5.81, p<.05
University degree: n (%)	3 (15)		1 (5)		
Employment status					
Student; n, (%)	19 (95)		20 (100)		
Employed; n (%)	1 (5)		0 (0)		
Unemployed; n (%)	0 (0)		0 (0)		
Ravens SPM (max 60)	48.15	5.00	49.40	4.89	0.64, p>.05
Letter Span	4.95	1.23	4.90	1.25	0.02, p>.05
Spatial Span	4.75	1.02	4.65	0.67	0.13, p>.05
Sleep Indices					
Sleep – Hours/night	6.90	1.49	8.15	1.78	5.77, p<.05
ESS Score (maximum 24)	6.95	3.07	6.10	3.01	0.78, p>.05
KSS before	5.32	1.49	4.15	1.35	Time: F(1,34) = 2.60, p>.05
KSS after	6.00	1.37	4.74	1.88	Time*group: F(1,34) = 0.20, p>.05 Group: F(1,34) = 12.49, p<.001
MEQ total	40.00	9.54	44.80	9.21	2.62, p>.05
Mood Adjective Checklist:					
Anxiety	7.95	2.63	7.85	2.39	0.02, p>.05
Depression	9.35	2.08	8.35	2.41	1.97, p>.05
Arousal	16.60	3.49	19.35	3.38	6.42, p<.01
NASA-TLX Letter					
Mental Demand	78.28	19.50	77.89	14.90	0.01, p>.05
Physical Demand	14.67	23.87	11.05	17.62	0.27, p>.05
Temporal Demand	60.33	26.93	59.11	27.00	0.02, p>.05
Effort	65.00	26.05	75.28	14.18	2.16, p>.05
Performance	48.06	22.12	53.33	21.71	0.52, p>.05
Frustration	49.17	26.01	39.72	22.15	1.38, p>.05
NASA-TLX Spatial					
Mental Demand	85.84	14.06	75.00	21.59	3.36, p = 0.07
Physical Demand	17.11	24.93	15.21	17.17	0.07, p>.05
Temporal Demand	59.11	26.51	56.16	30.73	0.10, p>.05
Effort	76.74	24.70	78.74	13.07	0.10, p>.05
Performance	41.37	20.23	47.95	21.45	0.95, p>.05
Frustration	52.21	22.63	40.26	20.65	2.89, p>.05

Table 2: Indices of Other drug use in ecstasy users, polydrug users and nonusers

	Ecstasy Users			Drug Naive		
	M	**SD**	**n**	**M**	**SD**	**n**
Ecstasy						
Frequency (times/wk)	0.39	0.48	20	-	-	-
Last 30 days (tablets)	3.80	4.60	20	-	-	-
Total use (tablets)	1305.31	4951.61	20	-	-	-
Length of Use (weeks)	176.12	157.90	20	-	-	-
Time since last use (weeks)	8.67 (median 2.5)	13.85 (range 47.29)	20	-	-	-
Cannabis						
Frequency (times/wk)	2.28	2.86	16	-	-	-
Last 30 days (joints)	33.81	57.61	16	-	-	-
Total use (joints)	4183.42	6353.33	16	-	-	-
Length of Use (weeks)	304.12	166.01	18	-	-	-
Time since last use (weeks)	16.40 (median 2)	60.83 (range 259.86)	16	-	-	-
Cocaine						
Frequency (times/wk)	0.32	0.47	12	-	-	-
Last 30 days (lines)	9.38	26.30	13	-	-	-
Total use (lines)	964.63	2876.88	14	-	-	-
Length of Use (weeks)	153.96	143.52	15	-	-	-
Time since last use (weeks)	19.32 (median 4)	22.65 (range 51.14)	13	-	-	-
Ketamine						
Frequency (times/wk)	0.39	0.79	6	-	-	-
Last 30 days use (grams)	1.2	2.68	5	-	-	-
Total use (grams)	118.73	249.71	9	-	-	-
Length of Use (weeks)	66.27	124.55	11	-	-	-
Time since last use (weeks)	52.64 (median 12)	83.13 (range 281)	11	-	-	-
Alcohol units p/w	23.05	28.00	20	8.33	6.15	20
Alcohol time since last use	0.79	1.30	20	0.63	0.44	20

% ever tried:		
Alcohol	100	100
Amphetamine	40	0
Cannabis	85	0
Cocaine	75	0
DMT	10	0
Ketamine	55	0
LSD	25	0
Mushrooms	30	0
Poppers	40	0
Salvia	20	0
Mephedrone	60	0

Table 3: Mean Oxy and deoxy Hb Change (μm)

	Ecstasy Polydrug Users		Nonusers		Main Analysis		ANCOVA	
	Mean	**SD**	**Mean**	**SD**	**F**	**p**	**F**	**p**
Spatial Updating					**(1,32)**		**(1,28)**	
LDLPFC-OXY	.94	1.26	.85	1.09	0.00	>.05	0.00	>.05
LPFC-OXY	.87	1.56	.02	1.14	0.20	>.05	2.73	>.05
RPFC-OXY	.75	1.31	.24	1.13	0.01	>.05	0.21	>.05
RDLPFC-OXY	.30	1.23	.36	1.08	0.31	>.05	0.00	>.05
LDLPFC-DEOXY	.37	.91	.44	1.18	1.99	=.08	0.15	>.05
LPFC-DEOXY	.06	1.15	.58	.99	0.60	>.05	1.36	>.05
RPFC-DEOXY	.21	.67	.33	.96	0.95	>.05	1.07	>.05
RDLPFC-DEOXY	-.14	1.44	.26	.93	0.95	>.05	0.83	>.05
Letter Updating					**(1,33)**			
LDLPFC-OXY	.22	1.14	.28	1.22	0.03	>.05	0.01	>.05
LPFC-OXY	.21	1.17	-.05	1.38	0.37	>.05	0.36	>.05
RPFC-OXY	.45	1.57	-.40	1.36	2.95	<.05	2.03	<.05
RDLPFC-OXY	.77	1.49	.35	1.17	1.02	>.05	2.52	>.05
LDLPFC-DEOXY	.38	1.38	-.33	1.17	2.51	=.06	3.33	=.09
LPFC-DEOXY	.44	1.25	-.60	1.22	6.24	<.01	8.49	<.01
RPFC-DEOXY	.47	1.42	-.71	1.09	6.71	<.01	7.43	<.01
RDLPFC-DEOXY	.47	1.44	-.38	1.03	6.26	<.05	7.21	<.01

Table 4: Correlations between drug use, background variables and haemodynamic changes

	RPFC-OXY	LDLPFC-DEOXY	LPFC-DEOXY	RPFC-DEOXY	RDLPFC-DEOXY
Ecstasy					
Frequency (times/wk)	.313*	.200	.278*	.334*	.275
Lifetime dose (tablets)	.182	.119	.226	.286*	.206
Current use (last 30 days)	.364*	.289*	.482**	.506**	.428**
Cannabis					
Frequency (times/wk)	.305*	-.036	.177	.237	.141
Lifetime dose (joints)	.355*	-.060	.139	.210	.116
Current use (last 30 days)	.317*	-.018	.212	.261	.180
Cocaine					
Frequency (times/wk)	.129	.058	.047	.055	.052
Lifetime dose (grams)	.216	.095	.126	.195	.147
Current use (last 30 days)	.147	-.174	-.109	-.072	-.124
Ketamine					
Frequency (times/wk)	.321*	-.100	.045	.151	.044
Lifetime dose (grams)	.257	-.016	.167	.228	.119
Current use (last 30 days)	-.119	.068	-.017	-.034	-.034
Average weekly alcohol (UK units)	.026	.012	-.003	-.033	-.013
Age (years)	.003	-.061	-.177	-.119	-.130
Average sleep per night (hours)	.109	.135	.194	.014	.166

Figure 1: Mean items correctly recalled on spatial and letter updating.

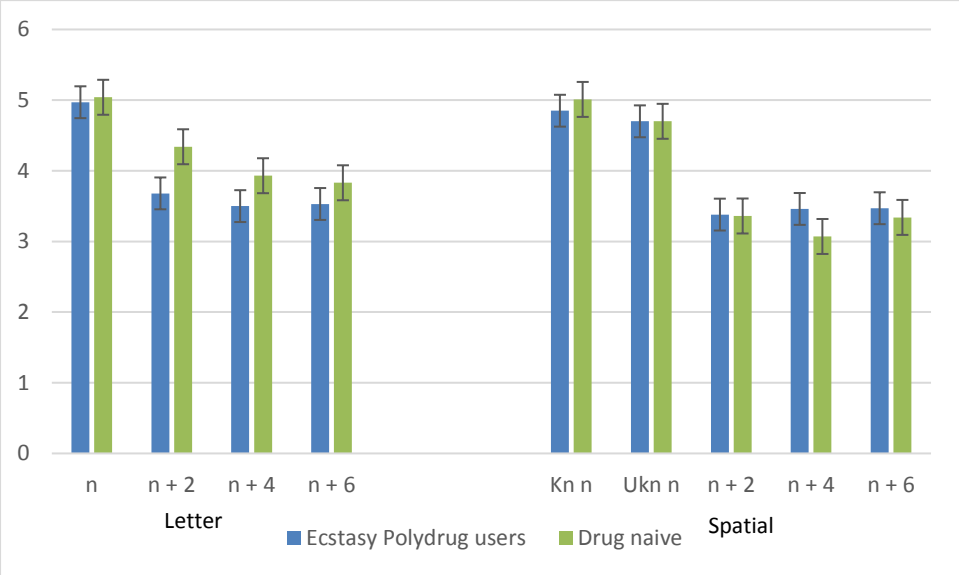

Figure 2: Mean cortical oxygenation and deoxygenation changes (µm) during Spatial and Letter Updating in the ecstasy-polydrug users and nonusers.